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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/734,472 | 12/12/2003 | Marc F. Charette | JJJ-P02-510 | 9598 |

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FISH & NEAVE IP GROUP
ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

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| EXAMINER |
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WANG, CHANG YU

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| ART UNIT | PAPER NUMBER |
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1649

DATE MAILED: 05/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|------------------------|---------------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 10/734,472 | CHARETTE, MARC F. | |
| | Examiner | Art Unit | |
| | Chang-Yu Wang | 1649 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on June 17, 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 27-38 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 27-38 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>2/12/04, 6/17/04</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of Application

Claims 27-38 are pending and under examination in this office action.

Priority

The instant application claims a method for reducing memory dysfunction associated with damaged hippocampal tissues comprising contacting a hippocampal cell with a morphogen comprising residues 330-431, 30-292, 48-292, 292-330, 292-431 or 30-431 of SEQ ID NO:2. The morphogens comprising residues 292-330, 292-431 or 30-431 of SEQ ID NO:2 as recited in the claims 33-35 are not presented in the application No. 09/012846, filed Jan 23, 1998, and thus considered as new matters. The specification only discloses a morphogen comprising residues 330-431, 30-292, or 48-292 of SEQ ID NO:2." (see p.12 in the specification).

Therefore, the priority for the subject matter to the extent of residues 292-330, 292-431 or 30-431 of SEQ ID NO:2. is Dec, 12, 2003.

Information Disclosure Statement

The information disclosure statement filed February 12, 2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all

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other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Oath/Declaration

"A continuation or divisional application filed under 37 CFR 1.53(b) (other than a continuation-in-part (CIP)) may be filed with a copy of the oath or declaration from the prior nonprovisional application. See 37 CFR 1.63(d)(1)(iv)." "If the examiner determines that the continuation or divisional application contains new matter relative to the prior application, the examiner should so notify the applicant in the next Office action. The examiner should also (1) require a new oath or declaration along with the surcharge set forth in 37 CFR 1.16(e); and (2) indicate that the application should be redesignated as a continuation-in-part." See MPEP§ 602.05.

This application presents a claim for subject matter not originally claimed or embraced in the statement of the invention. The specification only discloses a morphogen comprising residues 30-292, 330-431, or 48-292 of SEQ ID NO:2. A supplemental oath or declaration is required under 37 CFR 1.67. The new oath or declaration must properly identify the application of which it is to form a part, preferably by application number and filing date in the body of the oath or declaration. See MPEP §§ 602.01 and 602.02.

Therefore, a new oath or declaration is required.

Specification

The specification is objected to because it does not describe the claimed subject matter. The amendment filed Dec 12, 2003 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The morphogens comprising residues 292-330, 292-431 or 30-431 of SEQ ID NO:2 as recited in the claims 33-35 are not presented in the application No. 09/012846, filed Jan 23, 1998, and thus considered as new matters. The specification only discloses a morphogen comprising residues 330-431, 30-292, or 48-292 of SEQ ID NO:2." (see p.12 in the specification). Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for up-regulating the expressions of N-CAM and L1 in NG108-15 cells and increasing dendritic arbors of 7-14 DIV cultured hippocampal neurons with OP-1 (BMP-7) protein or in rats/mice, does not reasonably provide enablement for a method for reducing memory dysfunction associated with damaged

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hippocampal tissues comprising contacting a hippocampal cell with a morphogen comprising a conserved C-terminal seven-cysteine skeleton that is at least about 60% identical and 70% homologous to residues 330-431 of human OP-1 (SEQ ID NO:2) or fragments of SEQ ID NO:2 recited in the claims 29-35 as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

"There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is 'undue'. These factors include, but are not limited to:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)". See MPEP § 2164.01.

Claims 27-38 are drawn to a method for reducing memory dysfunction associated with damaged hippocampal tissue comprising contacting a hippocampal cell with a morphogen comprising a conserved C-terminal seven cysteine skeleton that is at least about 60% identical and 70% homologous to residues 330-431 of human OP-1 (SEQ ID NO:2) or regions of SEQ ID NO:2 as recited in the claims 29-35. Applicant discloses that 7-14 DIV cultured hippocampal neurons treated with OP-1 can induce dendritic arbor development. Applicant also discloses that the expressions of N-CAM and L1 in NG108-15 cells are upregulated after treating with OP-1. However, Applicant fails to demonstrate that treating a person/mammal with memory dysfunction due to hippocampal damage with OP-1 or fragments of OP-1 or related agents is able to reduce memory dysfunction in vivo. It is known in the art that the results derived from in vitro conditions do not reflect the results obtained from in vivo since the complexity of biological system. Several factors need to be considered to determine whether the in vitro findings can be applied to the in vivo condition. OP-1 or other morphogens as listed in the p1 in the specification and figure 1 may have activities to enhance neural development in vivo as disclosed in U.S. Patent No. 6723698. However, a reduction of memory dysfunction associated with damaged hippocampal tissues involves more than neural survival and dendritic development. It requires reconnecting the damaged neurons and reestablishing synaptic plasticity and cognitive function of the brain. Applicant fails to demonstrate that these morphogens are able to reduce memory dysfunction due to damaged hippocampal tissues in a patient or animal. In addition, it is known in the art that morphogens are important in axon guidance and have different

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activities due to their gradient effects in the brain (Charron et al. Development 2005. 132: 2251-2262). For example, Sonic hedgehog (Shh) needs to coordinate with BMP in cell fate determination and axon guidance. Shh functions as a chemoattractant for commissural axons to cross the midline and BMP7:GDF7 heterodimers mediate chemorepellent activity to collapse growth cone and guide commissural axons into the right trajectory in the developing spinal cord (p. 2253 and 2256). Applicant fails to teach how to use a morphogen comprising a conserved C-terminal seven-cysteine skeleton that is at least about 60% identity and 70% homologous to residues 330-431 of OP-1 or SEQ ID NO:2 or fragments recited in the claims 29-35 to reduce memory dysfunction in vivo. Applicant has not provided enough guidance as to enable one skilled in the art to make and/or use a morphogen as recited in the claims 27-35 to reduce memory dysfunction in vivo, indicating undue experimentation is required. In addition, Applicant may be enabled for using any morphogen comprising residues 30-292/330-431/48-292 of SEQ ID NO:2, which were disclosed in the U.S. Patent No. 6723698 or residues 292-431/ 30-431 of SEQ ID NO:2, which encompasses residues 330-431 of SEQ ID NO:2 to induce synapse formation in vitro or in vivo. However, Applicant fails to teach whether any morphogen comprising residues 292-330 of SEQ ID NO:2 has an activity to enhance neural development or synapse formation in hippocampal neurons or other neurons, indicating undue experimentation is required to practice the claimed invention.

Therefore, in view of the necessity of experimentation, the limited working examples, the unpredictability of the art, and the lack of sufficient guidance in the specification, it would require more undue experimentation to practice the claimed

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invention as it pertains to a method for reducing memory dysfunction associated with damaged hippocampal tissues comprising contacting a hippocampal cell with a morphogen comprising a conserved C-terminal seven cysteine skeleton that is at least 60% identical to and 70% homologous to residues 330-431 of human OP-1 (SEQ ID NO:2) or fragments recited in the claims 28-35.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 27-38 are rejected under 35 U.S.C. 102 (e) as being anticipated by U. S. Patent No. 6723698 (Rueger et al. issued on April 20, 2004, effective filing date September 25, 1997).

U. S. Patent No. 6723698 ('698) teaches a morphogen comprising at least 70% homology with C-terminal seven cysteine skeleton of human OP-1 residues 330-431 of SEQ ID NO:2 and a morphogen containing sequences greater 60% identity to the conserved C-terminal seven-cysteine motif including residues 330-431 of OP-1 can enhance dendritic development and synaptogenesis and useful

for potential treatment of several neurological disorders (column 13, lines 1-19). OP-1 enhances dendritic development and branches in hippocampal neurons in vitro. Cultured hippocampal neurons treated OP-1 have a dramatic increase of dendritic length and branches (see column 45, example 16, morphogen induce dendritic growth in various neurons:16.2 hippocampal neurons). In addition, OP-1 induces synaptogenesis in cultured hippocampal neurons vitro detected by MAP2 and synapsin antibodies (see column 50, example 17). '698 also teaches OP-1 induces synapstogenesis in hippocampal tissues in vivo (see column 50, example 18). '698 also teaches a method of improving motor function in mammals with symptoms of neural pathway damage in the peripheral nervous system and treating amyotrophic lateral sclerosis comprising administering the mammal with a morphogen comprising at least 70% homology with C-terminal seven cysteine skeleton of human OP-1 residues 330-431 of SEQ ID NO:2 or a morphogen containing sequences greater 60% identity to the conserved C-terminal seven-cysteine motif including residues 330-431 of OP-1 (see columns 69-72, claims 1-16). '698 further teaches morphogens for treatment selected from human OP-1, mouse OP-1, human OP-2, human OP-2, mouse OP-2, 60A, GDF-1, BMP2A, BMP2B, DPP, Vg1, Vgr-1, BMP3, BMP5 or BMP6. The sequence of OP-1 disclosed in '698 comprises the residues 30-292, 330-431, 48-292, 292-330, 292-431, and 30-431 of SEQ ID NO:2, which meets the limitations of the claims. Further, the sequences containing the residues 330-431 also anticipate the sequences containing the residues 292-431 or 30-431 of OP-1

(instant SEQ ID NO:2). Therefore, claims 27-38 are anticipated by U. S. Patent No. 6723698.

Claims 27-35 are rejected under 35 U.S.C. 102 (b) as being anticipated by Withers et al. (Society for Neuroscience Abstracts, (1997) Vol. 23, No. 1-2, pp. 1433. Treatment with osteogenic protein-1 increases synaptogenesis in cultured hippocampal neurons. 27th Annual Meeting of the Society for Neuroscience. New Orleans, Louisiana, USA. October 25-30, 1997. ISSN: 0190-5295.).

Withers et al. teach that OP-1 can increase dendritic outgrowth, branches and synaptogenesis in cultured hippocampal neurons (see abstract No. 565.20). Cultured hippocampal neurons were treated with OP-1 and OP-1 was able to induce synapse formation in 1-2 week cultured hippocampal neurons. In addition, OP-1 comprises the fragments of SEQ ID NO:2 recited in the claims 27-35. The reference teaches the procedures of the method, which meets the limitations of the claims. Therefore, claims 27-35 are anticipated by Withers et al.

Conclusion

NO CLAIM IS ALLOWED.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

U.S. Patent No. 6949505 issued Sep 27, 2005, effective filing date Aug 18, 1994.

U.S. Patent No. 6194376 issued Feb 27, 2001, effective filing date Aug 30, 1991.

U.S. Patent No. 6495513 issued Dec 17, 2002, effective filing date Jul 31, 1992.

U.S. Patent No. 6506729 issued Jan 14, 2003, effective filing date Jun 16, 1994
as cited by Applicant in IDS.

U.S. Patent No. 6723698 issued Apr 20, 2004, effective filing date Sep 25, 1997.

Withers et al. (Society for Neuroscience Abstracts, (1995) Vol. 21, No. 1-3, pp.
1542. Osteogenic protein-1 (OP-1) induces dendritic growth and branching in cultured
hippocampal neurons. 25th Annual Meeting of the Society for Neuroscience. San
Diego, California, USA. November 11-16, 1995. ISSN: 0190-5295, as cited by Applicant
in IDS).

Any inquiry of a general nature or relating to the status of this general application
should be directed to the Group receptionist whose telephone number is (571) 272-
1600.

Papers relating to this application may be submitted to Technology Center 1600,
Group 1649 by facsimile transmission. The faxing of such papers must conform with
the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should
applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-
8300.

Any inquiry concerning this communication or earlier communications from the
examiner should be directed to Chang-Yu Wang, Ph.D. whose telephone number is

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(571) 272-4521. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CYW
May 3, 2006


JANET L. ANDRES
SUPERVISORY PATENT EXAMINER